

Infective Causes of Fever and Thrombocytopenia among Indoor Patients in a Tertiary Care Hospital in Islamabad

Asif Irfan, Asma Zafar Khawaja, Muhammed Khalil, Savida Ilyas Dar, Muaz Mubashir, Aroosha Farid
Department of Internal Medicine, Federal Government Polyclinic Hospital, Islamabad

ABSTRACT

Objective. To identify infective causes of thrombocytopenia among indoor patients in a tertiary care hospital in Islamabad.

Methodology: All patients with documented fever of more than 3 days and platelets of less than 140,000/ml were included in the study. In total 147 patients of fever due to infective causes with thrombocytopenia were included, whereas patients with non-infective causes of thrombocytopenia were excluded. The patients were advised Blood CP, MP smear, ICT MP, Blood C/S, Dengue NS1, Dengue serology, Serology for leptospirosis and X-Ray chest. Statistical analysis was done using SPSS.

Results: Among 147 cases, 35% of patients were males and 45% were females. Mean age was 39.65±16 years. The maximum number of patients had a platelet count between 20,000-50,000. The largest number of patients presented with petechiae followed by those with gingival bleeds and epistaxis. The diseases diagnosed in order of frequency were Dengue, Enteric fever, Malaria, Sepsis with DIC, Brucella, Leptospirosis, Hepatitis A, Disseminated TB and HIV.

Conclusion: Infective causes of, which are fairly reversible with control of infection, should be kept in mind before embarking upon definitive and prolonged treatments of thrombocytopenia

Key words: Epistaxis, Gingival bleed, Petechiae, Thrombocytopenia.

Authors' Contribution:

^{1,2}Conception; Literature research; manuscript design and drafting; ^{2,3}Critical analysis and manuscript review; ^{5,6}Data analysis; Manuscript Editing.

Correspondence:

Savida Ilyas Dar
Email: savidadar@gmail.com

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Introduction

Thrombocytopenia, characterized by low platelet count may manifest as bleeding from skin, mucous membrane or bleeding from any other site, petechiae, bruises etc. The risk of spontaneous bleed increases with platelet count less than 20,000, whereas platelet less than 5000 put patient at higher risk of intracranial bleed. Among all causes of thrombocytopenia one of the most significant causes which is observed in daily practice is infective etiology, which improves with control of infection. Fever with thrombocytopenia is a common

presentation of patients admitted in the medical wards. Prior knowledge of the common diseases presenting with thrombocytopenia may be helpful in early diagnosis, appropriate investigation and prompt management of the patients.

Different sites for bleeding from thrombocytopenia can be skin, mucous membrane, upper and lower gastrointestinal bleed, hemoptysis, bleeding from genitourinary system and last but not the least being intracranial bleed. In a study done previously bleeding manifestations were present in 19.45 % of patients and the commonest sites were skin and

mucous membranes. Bleeding manifestations were seen most commonly in children with a platelet count less than $<20,000/\text{UI}$.^{1,2} Thrombocytopenia can manifest in all age groups but a common clinical trend towards younger age group has been observed with a relative male predilection with the mean age of 20-30 years.^{3,4} The diseases found to be most commonly associated with thrombocytopenia were dengue, enteric and typhus fever.⁵ Another study showed a more dominant prevalence of dengue fever especially in regions like Iran⁶. Wang WH has put even more stress on dengue hemorrhagic fever with special emphasis on its prevention and pathogenesis.⁷ karthikraj with his colleagues has studied dengue fever in children as cause of thrombocytopenia besides many other causes.⁸

Several studies have been conducted in the Sub-continent on correlation of infective diseases with thrombocytopenia but we could not find any such study in literature which has been done previously in our country.

Methodology

This study was conducted in the medical ward of Federal Government Polyclinic (FGPC) hospital, Islamabad over a period of 6 months from March 2019 to September 2019. Informed consent was taken from patients. All patients presenting with fever and thrombocytopenia were enrolled in the study. A detailed history and examination was done. The baseline tests of blood complete count (Blood CP), ESR, Urine routine examination (Urine RE) Liver function tests (LFTs), Renal function tests (RFTs), serum electrolytes (S/E) and X ray-chest were done. This was followed by investigations for the common causes of fever in our region. A blood complete picture for thrombocytopenia was done as inclusion criteria at admission, thick and thin blood films for malarial parasite (MP Smear) were done, The ICT for malaria (ICT-MP). Blood culture was sent for salmonella and other organisms. Dengue NS-I

antigen was done if the patient presented with in the first five days but serology for Dengue IgM and IgG if fever was of more than five days duration. If the patient had jaundice or conjunctival suffusion, serology for leptospirosis (IgM antibodies) was sent. Hepatitis A and E was done if the bilirubin and ALT were raised. If the fever was of a longer duration then the patient was tested for Brucellosis (Aborts and Melitensis). If there was history of contact the patient was screened for HIV. Disseminated Tuberculosis was picked up by doing an initial chest X-Rays and further bone marrow biopsy if indicated. All patients presenting with documented fever of more than 3 days and platelets of less than $140,000/\text{ml}$ were included in the study. Only cases of thrombocytopenia secondary to infective causes were enrolled in the study.

Following patients were excluded from the study:

- Diagnosed cases of thrombocytopenia, which were previously being followed up for their primary disease due to non-infective etiology.
- Patients who had bi-cytopenia or pancytopenia on Blood CP report.
- All previously diagnosed patients with a diagnosis of leukemias, lymphoproliferative or myeloproliferative disorder, vasculitis, autoimmune disorders, Immune thrombocytopenia or drug induced thrombocytopenia.
- Patients of chronic liver disease.
- The patients in whom a diagnosis could not be reached in spite of investigation for Pyrexia of Unknown origin with thrombocytopenia were not included in the analysis.

WHO calculator was used to calculate the sample size. The data was analyzed for frequency, percentage, mean and standard deviation. The stratification of the patients were also done according to the platelet count. The patients and the various bleeding sites were recorded. The data was analyzed using SPSS version 23.

Ethical approval for the study was obtained from the institutional review board of Federal Government Polyclinic Hospital, Islamabad, (Ref# FGPC.1/12/2020) on 18-10-2020.

Results

In total 147 patients presenting with fever and thrombocytopenia (with infective etiology) fulfilling the inclusion criteria, were enrolled in the study. Nine patients who had fever and thrombocytopenia but the cause was non infective, (5 of Leukemia, 2 of immune thrombocytopenia, 1 of vasculitis and 1 of autoimmune hepatitis) were excluded from the study.

Out of the 147 patients, 81(55%) were males and 66(45%) were females with the mean age of the patients was 39.65 + 16 years.

Maximum number of patients reported were those with dengue fever followed by enteric fever and Malaria, followed by sepsis with DIC, brucellosis, leptospirosis, Hepatitis A, Disseminated Tuberculosis, and HIV Infection as mentioned in Table I.

The maximum number of patients had a platelet count between 20 and 50 thousand. Further distribution is seen in Table II.

Most of the patients presented with petechiae followed by those with gum bleed and epistaxis. Further presentations of thrombocytopenia are demonstrated. (Table III)

Causes	No. of cases	percentage%
Dengue fever	59	35.90
Enteric fever	34	20.79
Malaria	29	18.90
Sepsis with DIC	7	4.20
Brucellosis	5	3.04
Leptospirosis	5	2.43
Hepatitis A	3	1.82
Disseminated TB	2	1.21
HIV infection	2	1.21
Total	147	100

Platelets	No of patients	%
0-10000	3	2.04
10000-20000	8	5.44
20000-50000	46	31.29
50000-75000	30	20.48
75000-100000	48	32.65
100000-140000	12	8.16

Bleeding	no of patients
Petechiae	38
Gum bleed	21
Epistaxis	9
Ecchymosis	7
Hematuria	2
Hemoptysis	1

Discussion

The region of the subcontinent comes partly in the tropics and partly in the temperate regions. The weather and the terrain have major fluctuations from hot deserts to the frozen Himalayas. This weather and range of temperature give an adequate room to growth of all sort of infection most of which do not manifest alone with fever but also with thrombocytopenia. Many studies have been done in subcontinent region though not particularly in Pakistan. The basic goal behind all of them has been the same that is to look into infective causes of thrombocytopenia before embarking upon complicated diagnosis and starting long term treatment like steroids, immunoglobulins and splenectomy. We conducted the study in our country with same intention so as to prevent the patient as well as clinician to enter into an exhaustive journey for a fairly reversible cause of thrombocytopenia Our study was conducted between the months of March 2019 to September 2019, when the weather starts to warm up and all vectors reappear after the winter hibernation. Among many other studies, coinfection with two viruses was found in a study in 26% of cases, wherein

patients were found to have coinfection of dengue and chikungunya.³ Both of them were found to be associated with thrombocytopenia especially the dengue fever. In another study where malaria was found as the predominant cause of fever and thrombocytopenia, among all the malarial species *P. Falciparum* was found in 54% of cases.³ 'Sepsis' as a cause of fever and thrombocytopenia was found a major factor in two other studies.^{5,7} Dengue fever seems to be one of leading causes of infection with thrombocytopenia. It is found to be the most common among first three diagnosis which are dengue, enteric fever and malaria. This predominance of dengue was found in all the studies from the subcontinent.⁷ Pesticide resistance may be one factor that these mosquitos borne diseases are still endemic and occurs as pandemics too. This also highlights the inability to develop an effective vaccine for the centuries old malaria or the newly devastating infection of dengue fever.^{8,9} Besides these commonly reported infections of dengue, malaria and enteric several other infections like leptospiral, brucella and Hepatitis A were found to be prominent in our study. *Leptospira* has also been reported by Kristine et al.,⁹ Likewise Chikungunya has also been reported by the same author as one of causes of fever and thrombocytopenia.⁹ Unfortunately we could not identify and report scrub typhus because of non-availability of serology in our setup. The same limitation was experienced by few other authors conducting study in our region.⁹ The only indirect clue to scrub typhus was the response to vibramycin, which was interpreted as evidence for the presence of Rickettsial infection, when all other possible infection had been excluded for which, diagnostic tools were available. We know from our literature review that Rickettsial infections are common in Malaysia and other far east countries.¹¹ The vector *Orientia tsutsugamushi* has also been identified in North India.¹² That evidence in surrounding countries can be extended as a logic for presence of shrub typhus in our country as well. The seroprevalence trends have been studied in

India.¹³ So we believe that the testing facilities must be available in our country as well we may miss the diagnosis. With all these limitations we can conclude that Rickettsial diseases like scrub typhus are among the most under diagnosed and neglected infections especially in cases where we can't find a plausible diagnosis.¹³

Dengue fever starting from-being an unknown virus during the first epidemic in 1953-54 in Philippines was seen to be increasing to a figure of 100 million cases of dengue fever, 500000 cases of DHF and 25000 deaths per year by the year 1998¹⁴. Malaria is the centuries old *Plasmodium* infection that has not decreased with the advancements in medical care and is still among the top three diagnoses. In a study by Meena R, dengue and malaria have been found to be the most common cause of fever associated with fever and thrombocytopenia.¹⁵

As quite comparable with other studies in our region the top three diagnosis remain the same in our study as well with dengue being the leading cause and enteric and malaria following it. Most of the patients have a platelet count between 20-50 thousand with most common bleeding manifestation being petechiae. We found HIV in 1% of cases with no case reported for Congo fever. Keeping all these results in mind, as well as analyzing other studies done in the same context, we can look forward to a better management of thrombocytopenia which can be cost effective as well as time effective in a resource poor country like us.

We can expect more studies to be done under the same umbrella but with a new direction added to it.

Conclusion

By this study we reach a conclusion that there is a significant proportion of patients with thrombocytopenia secondary to infections. We should look into all infective causes of thrombocytopenia before embarking upon definitive treatment of thrombocytopenia. We look forward to further studies in our region in this regard

so that this over treated condition maybe addressed in a more rational way.

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